CHIẾN LƯỢC GIẢM ĐỘT TỬ TRONG SUY TIM

TS.BS Tôn Thất Minh
GĐ Bệnh viện tim tâm đức TP HCM
Hue 07.2019

Disclosure

Presenter's Name: Ton That Minh

• Employed as **Director of Tam Duc Heart Hospital and lecturer at Pham Ngoc Thach Medicine University**

Relevant Nonfinancial Relationships:

• Societies member – **VNHA, HCMCA, VN ICA, South ICA**

Last 12 month Relevant Financial Relationships:

Receives a financial support for speaking and traveling from **Astra-Zeneca, Medtronic, Biotronic, Boehringer, Sanofi, MSD, Novartis, Servier, Pfizer.**

This presentation is supported by Novartis.

References for this presentation will be provided if required.

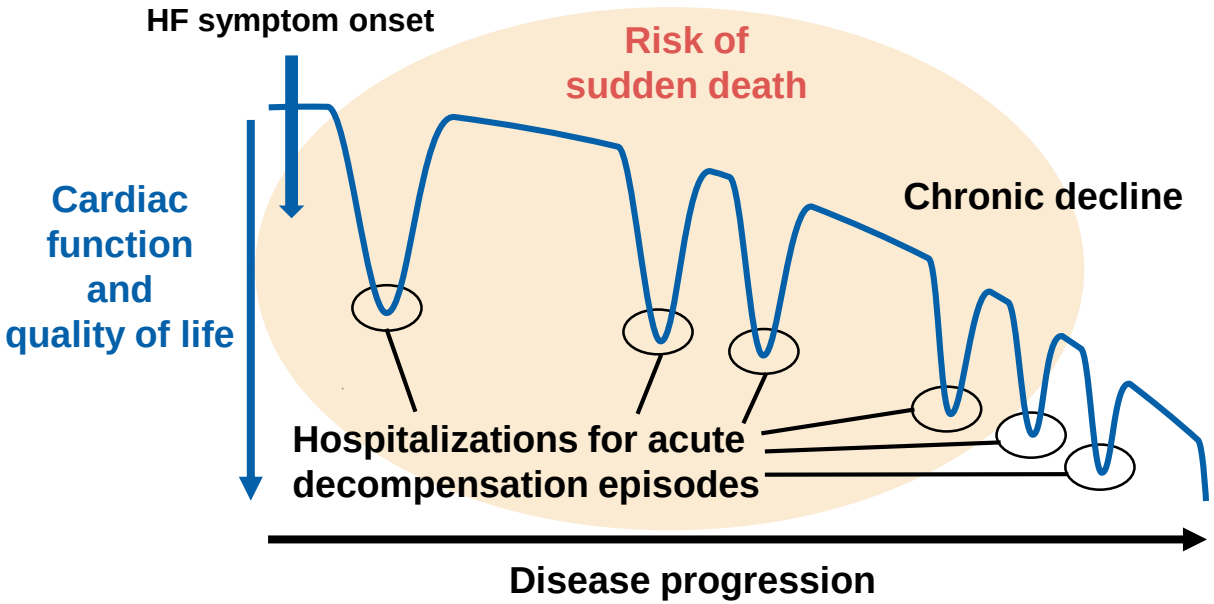
NỘI DUNG

1. Khái niệm suy tim ổn định
2. Khuyến cáo phòng ngừa đột tử
3. ARNI chiến lược giảm đột tử trong suy tim
4. Kết luận

Suy tim là một bệnh tiến triển

Sự thoái triển cấu trúc và chức năng tim xảy ra ngay trong giai đoạn sớm

- Bệnh nhân suy tim có nguy cơ đột tử trong suốt quá trình bệnh (5,6).
- Đột tử có tỷ lệ lớn hơn ở bệnh nhân trẻ tử vong với suy tim nhẹ, hơn khi bệnh suy tim tiến triển (6-8).



NYHA không là chỉ số duy nhất đánh giá tính ổn định

- **Nhóm bệnh nhân ít triệu chứng chưa được chú ý đúng mức**
- **Đa số bác sĩ suy nghĩ rằng NYHA II / ít triệu chứng không phải nhóm nguy cơ cao**
- **Triệu chứng chưa được khai thác kỹ để đánh giá**
- **"bệnh nhân không than phiền / ít than phiền có nghĩa là bệnh nhân ổn định"**

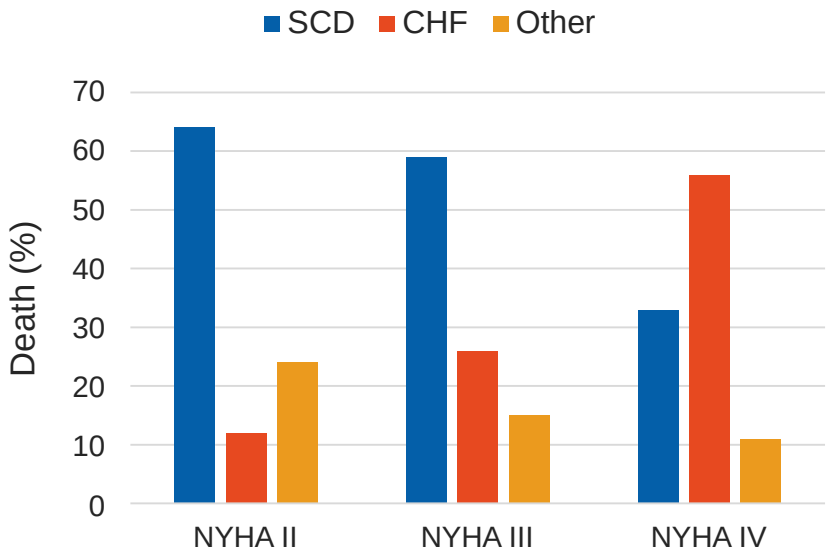
Định nghĩa thế nào là một bn suy tim ổn định?

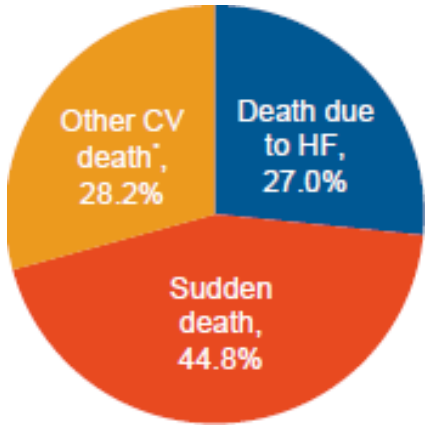
- ***Triệu chứng ổn định, không xấu đi* với NYHA I-II từ lần xuất viện trước?**
- **Bệnh nhân đã "quen" với thuốc cũ?**
- **3 tháng, 6 tháng, 12 tháng... gần đây *chưa cần nhập viện*?**

Không có suy tim ổn định:

NYHA II vẫn tiếp tục tử vong

- *MERIT HF post hoc analysis*: the incidence of SCD is higher in patients with less severe HF (NYHA class II), although total mortality rates increase with higher NYHA class[1]
- *PARADIGM-HF analysis*: 44.8% of NYHA class II HF CV deaths were SCDs[2]





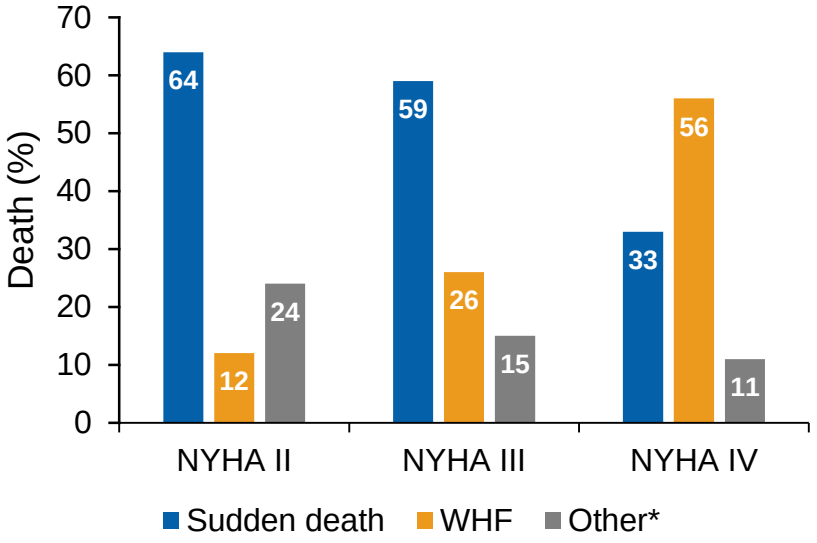
**Other CV death includes all CV deaths not ascribed to pump failure or sudden death*

CV, cardiovascular; HF, heart failure; MERIT-HF, Metoprolol CR/XL Randomised Intervention Trial in-Congestive Heart Failure; NYHA, New York Heart Association; PARADIGM-HF, Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure;SCD, sudden cardiac death; CHF, congestive heart failure

1.MERIT-HF Study Group. Lancet. 1999;353(9169):2001–7;
2. Desai AS et al. Eur Heart J. 2015;36:1990–7

Bệnh nhân suy tim NYHA II có nguy cơ cao bị đột tử

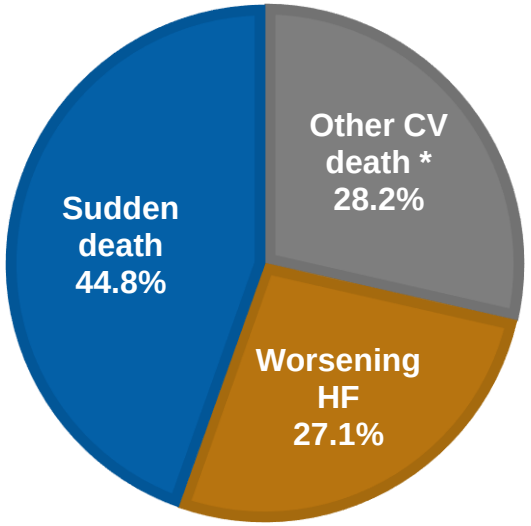
Sự thoái triển cấu trúc và chức năng tim xảy ra ngay trong giai đoạn sớm



*Other death includes all CV deaths not ascribed to WHF or sudden death

A post-hoc analysis from MERIT-HF (n=3,991)[1]
Mean follow up, 1 year

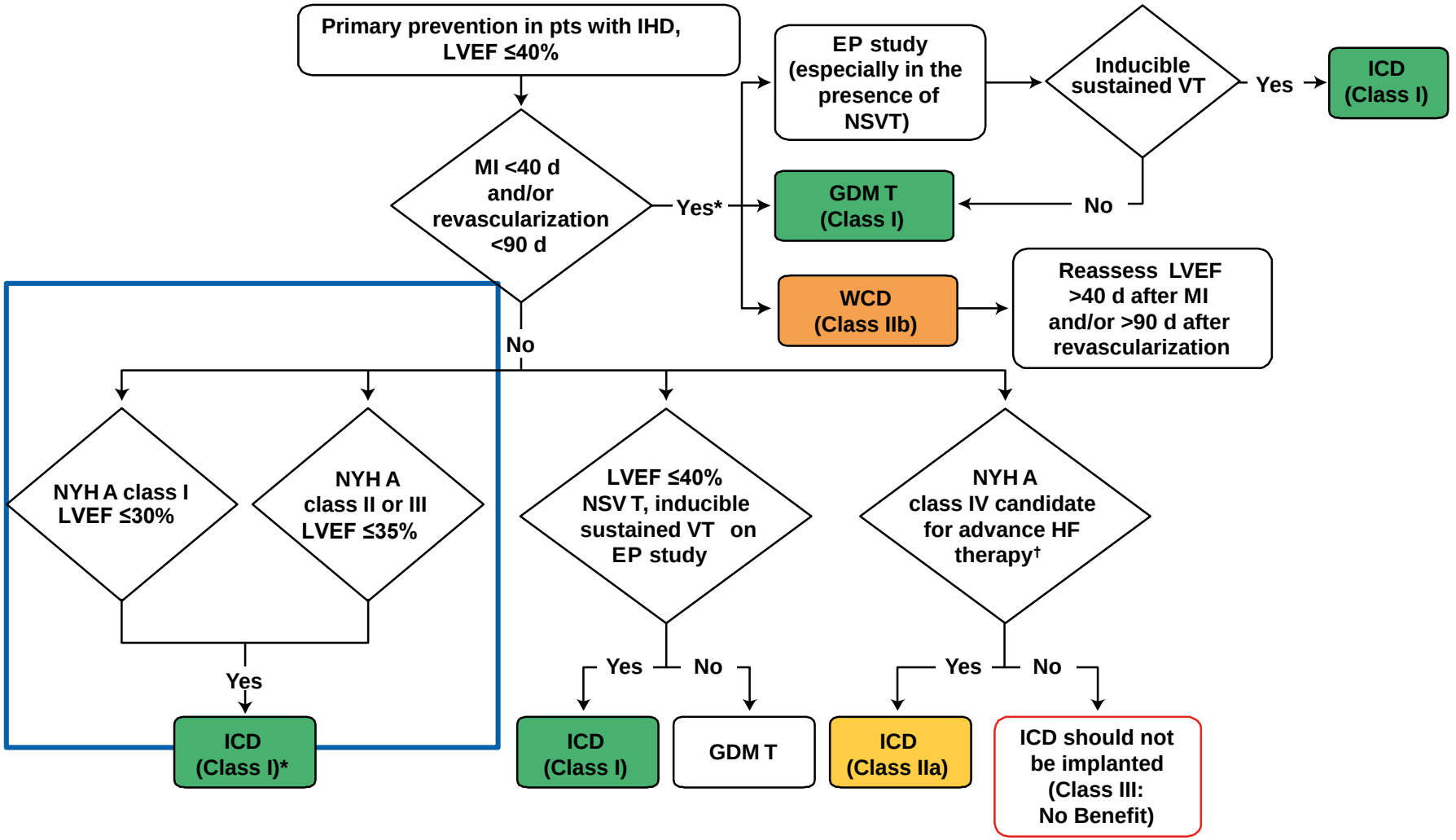
NYHA class II:
Mode of CV death
N=791



*Other CV death includes all CV deaths not ascribed to pump failure or sudden death

An analysis from PARADIGM-HF (n=8,399)[2]
Median follow up, 2.3 years

Phòng ngừa tiên phát đột tử do tim ở BN bệnh động mạch vành



2016 ESC: Khuyến cáo phòng ngừa đột tử

Recommendations for implantable cardioverter-defibrillator in patients with heart failure		
Recommendations	**Class**	**Level**
An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients with symptomatic HF (NYHA Class II–III), and an LVEF ≤35% despite ≥3 months of OMT, provided they are expected to survive substantially longer than one year with good functional status, and they have:		
IHD (unless they have had an MI in the prior 40 days)	**I**	**A**
DCM	**I**	**B**

Recommendations for the management of ventricular tachyarrhythmias in heart failure[1]		
Recommendations	**Class**	**Level**
Treatment with beta-blocker, MRA and sacubitril/valsartan reduces the risk of sudden death and is recommended for patients with HFrEF and ventricular arrhythmias	**I**	**A**

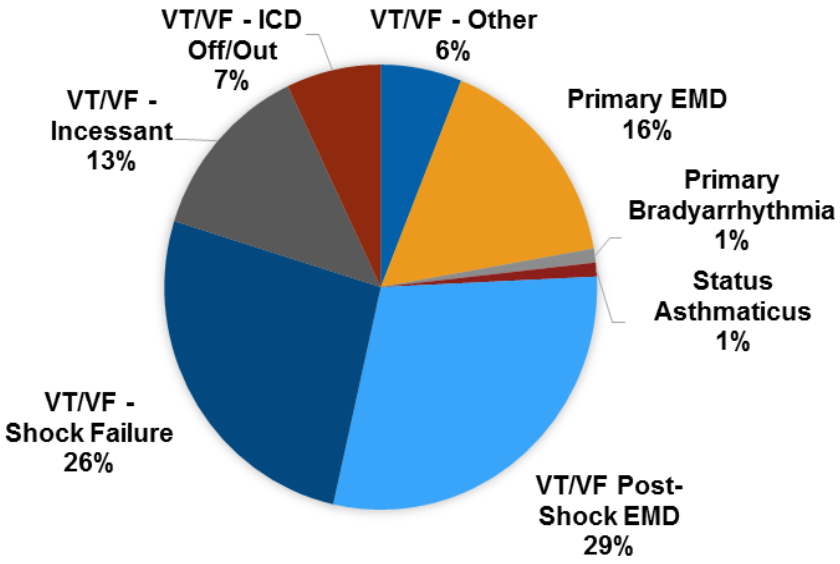
2017 AHA/ACC/HRS: Khuyến cáo phòng ngừa đột tử

Recommendations for Primary Prevention of SCD in Patients With Ischemic Heart Disease		
Recommendations	**Class**	**Level**
1. In patients with LVEF of 35% or less that is due to ischemic heart disease who are at least 40 days' post-MI and at least 90 days postrevascularization, and with NYHA class II or III HF despite GDMT, an ICD is recommended if meaningful survival of greater than 1 year is expected	**I**	**A**
2. In patients with LVEF of 30% or less that is due to ischemic heart disease who are at least 40 days' post-MI and at least 90 days postrevascularization, and with NYHA class I HF despite GDMT, an ICD is recommended if meaningful survival of greater than 1 year is expected	**I**	**A**

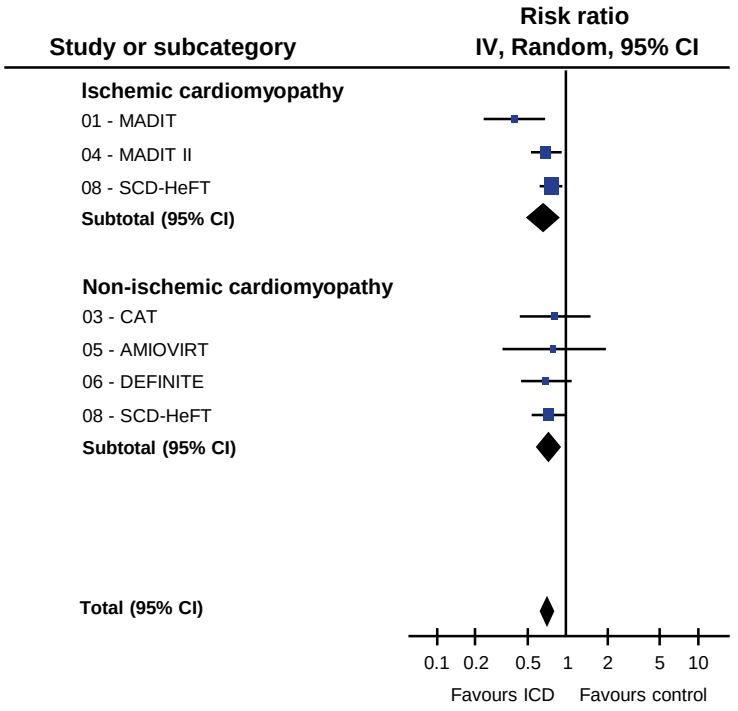
Recommendations for pharmacological prevention of SCD[1]		
Recommendations	**Class**	**Level**
In patients with HFrEF (LVEF ≤40%), treatment with a beta blocker, MRA and either an ACEI, ARB, or an angiotensin receptor neprilysin inhibitor is recommended to reduce SCD and all-cause mortality	**I**	**A**

Đột tử vẫn còn xảy ra dù BN được đặt máy ICD

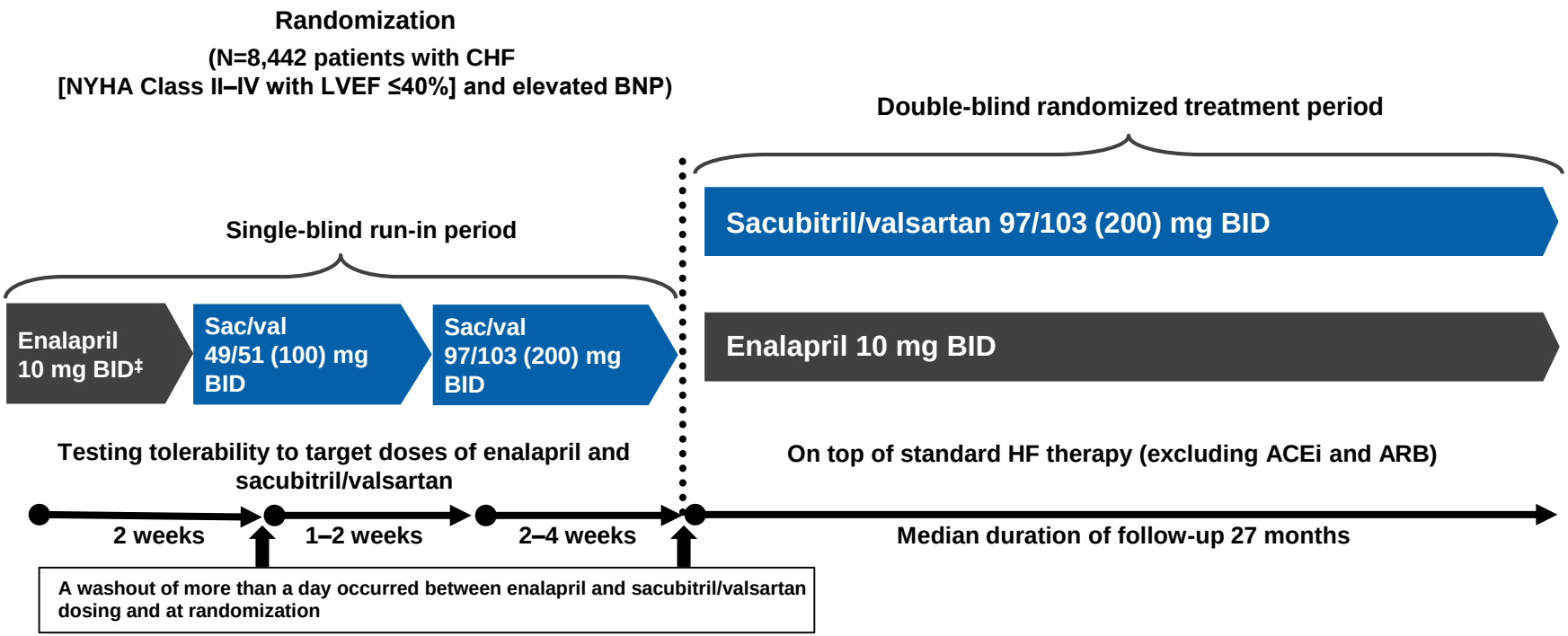
- In a review of 320 patient deaths during trials of ICD systems, the most common mechanism of sudden death in patients with an ICD was VT/VF treated with an appropriate shock followed by EMD[1]



- In an analysis of trials of ICD systems, greater absolute benefit was found in patients with ischemic heart disease compared with dilated cardiomyopathy[2]

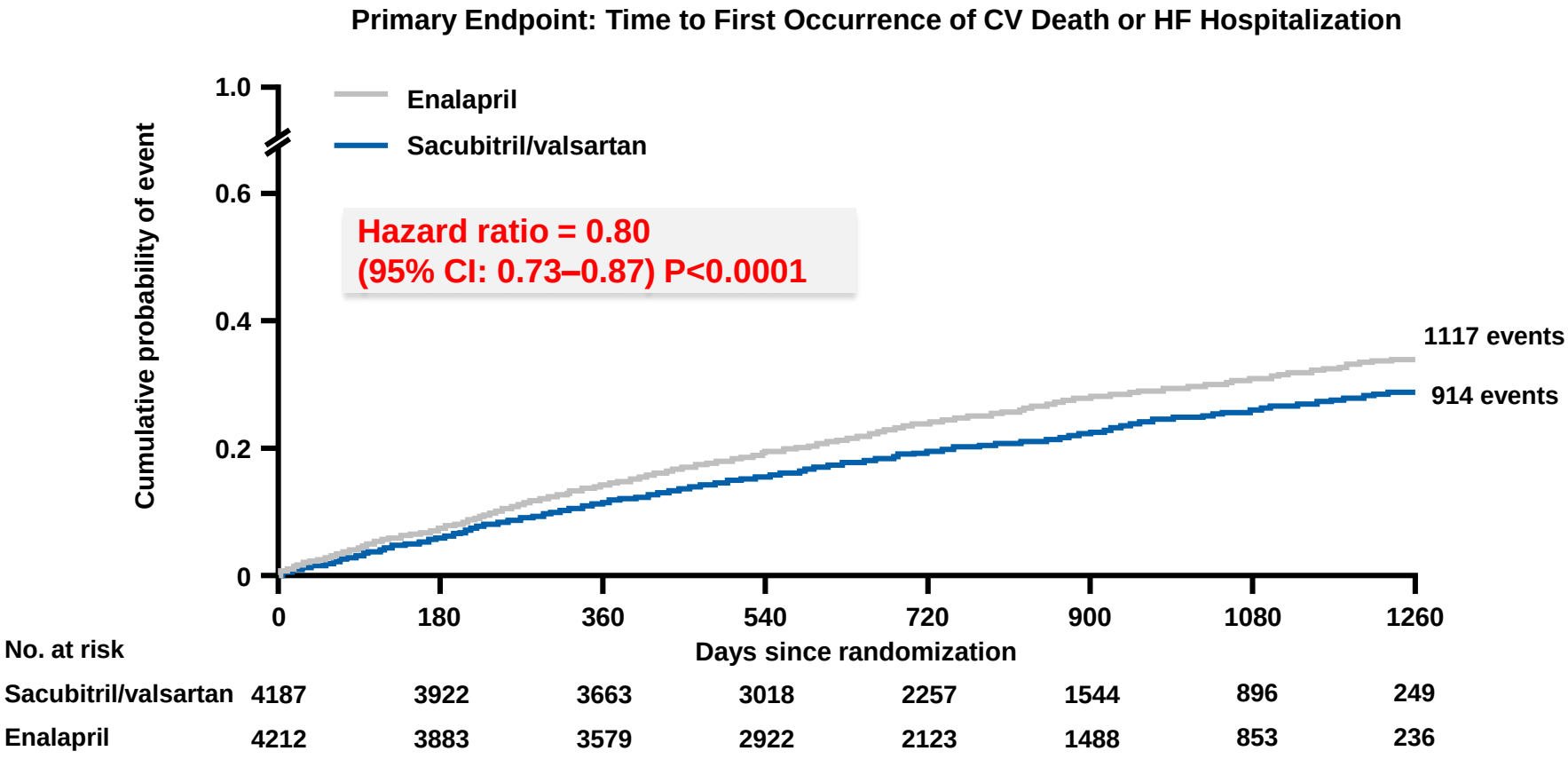


Nghiên cứu PARADIGM-HF

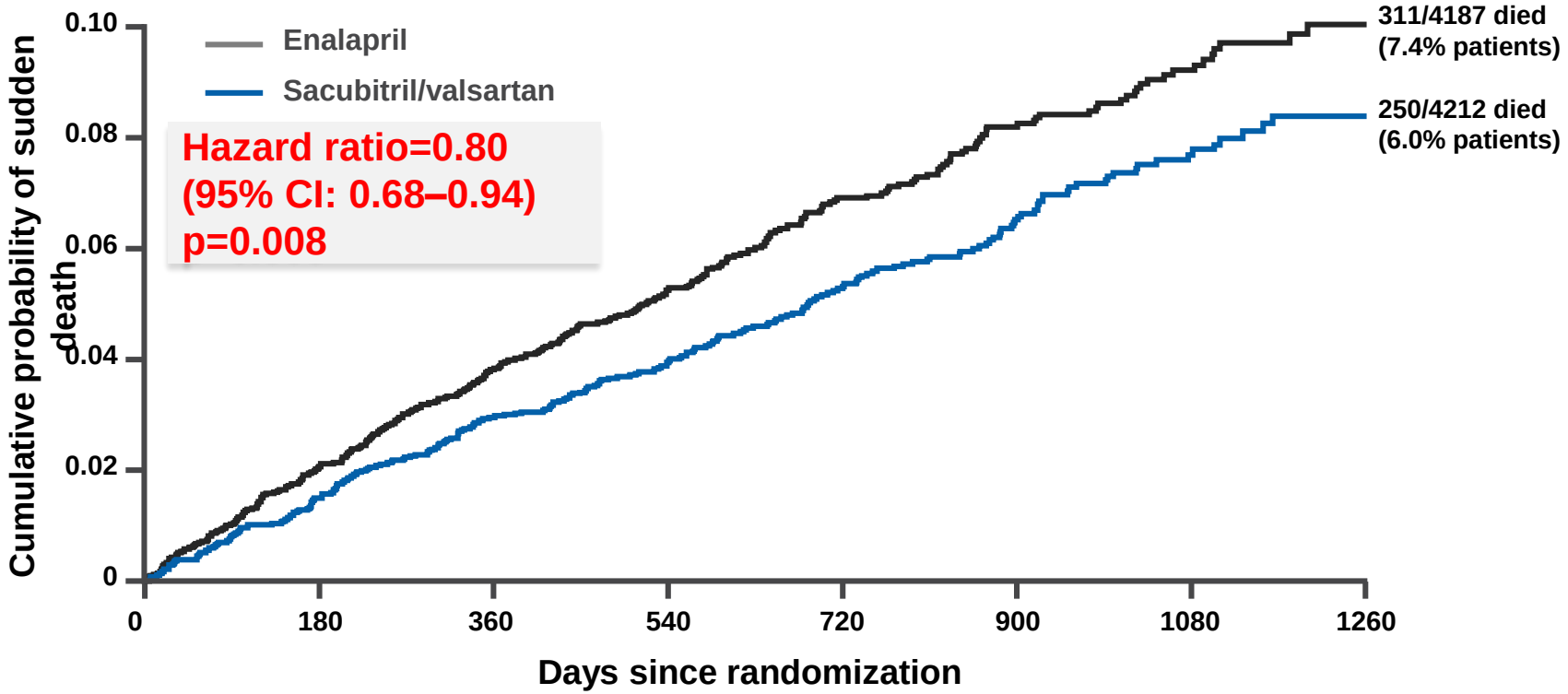


‡Enalapril 5 mg BID for 1–2 weeks followed by enalapril 10 mg BID as an optional starting run-in dose for patients who are treated with ARB or with a low dose of ACEi.

PARADIGM-HF: Sacubitril/valsartan giảm tiêu chí chính



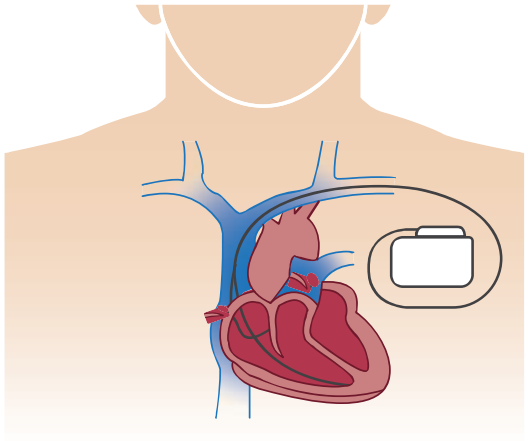
Sacubitril/valsartan làm giảm đáng kể đột tử so với enalapril



No. at risk				
Sacubitril/valsartan	4187	3891	2478	1005
Enalapril	4212	3860	2410	994

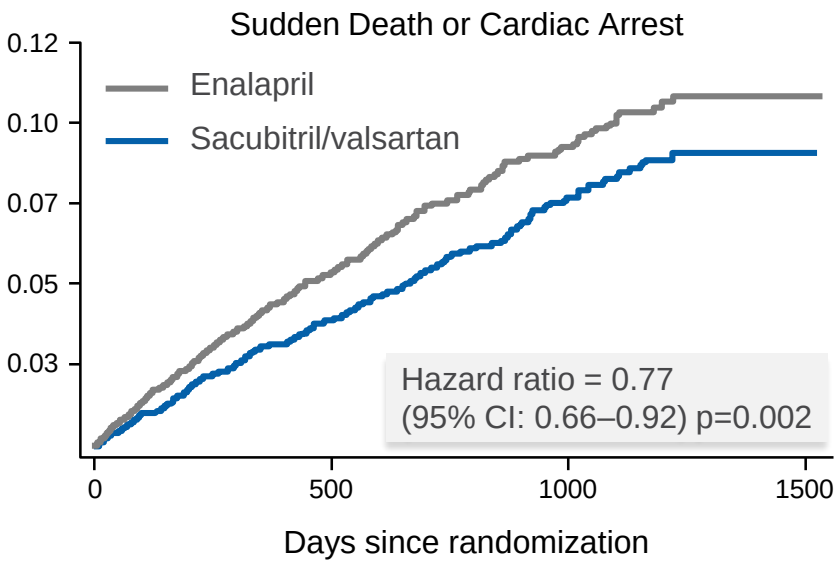
Lợi ích giảm đột tử của sacubitril/valsartan độc lập với ICD

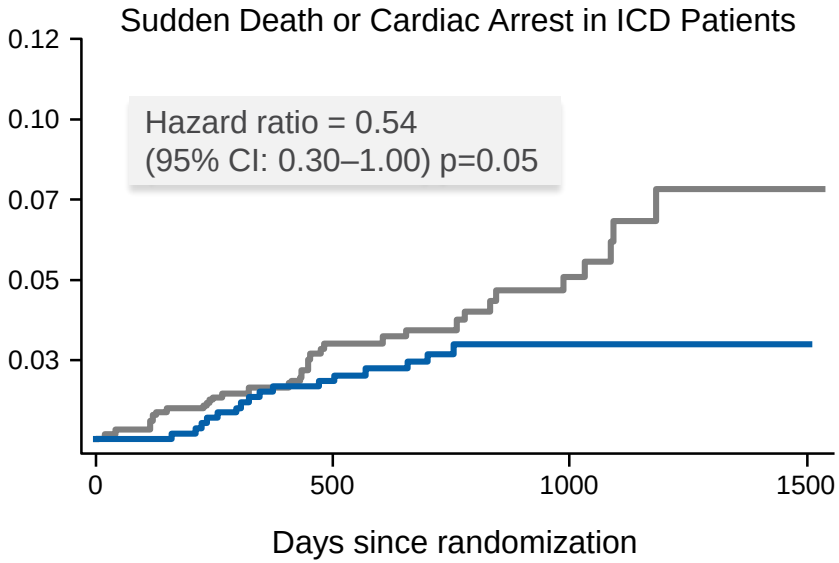
- ICD and CRT-D use in PARADIGM-HF was 15% and 5%[1,2] respectively, similar to that in other recent HFrEF trials.[3,4] While the patients with an ICD had a lower overall risk of sudden death, their use did not eliminate risk completely
- The sacubitril/valsartan treatment effect on sudden death was not influenced by the presence of defibrillator devices[2]
- Among patients with an ICD, use of sacubitril/valsartan reduced the relative risk of sudden death by 51% compared with enalapril[2]



PARADIGM-HF	Sudden death n (%)	Hazard ratio, sac/val vs. enalapril (95% CI)
– ICD	7.3% (525/7156)	0.82 (0.69–0.98)
Enalapril*	8% (287/3592)	n/a
Sac/val*	6.7% (238/3564)	n/a
+ ICD	2.9% (36/1243)	0.49 (0.25–0.98)
Enalapril*	3.9% (24/620)	n/a
Sac/val*	1.9% (12/623)	n/a

Sacubitril/valsartan làm giảm nguy cơ đột tử hay ngưng tim so với enalapril, bất chấp ICD





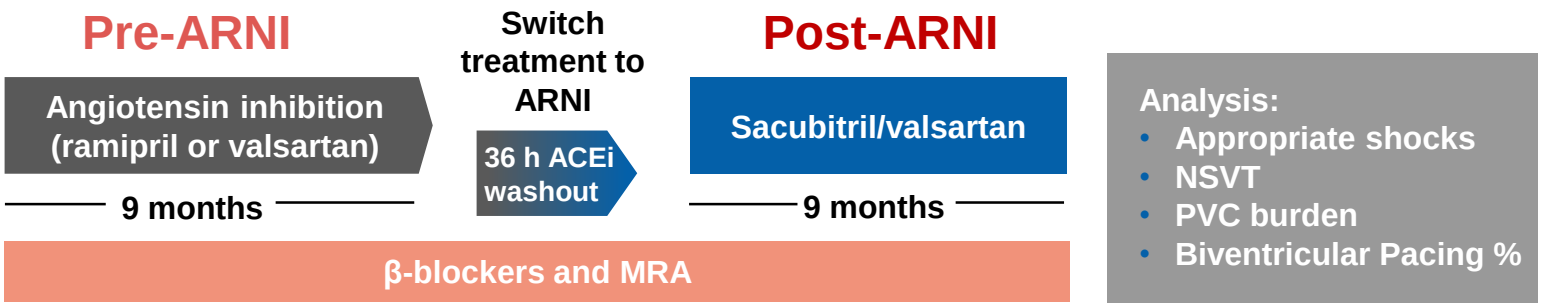
P-interaction for efficacy of sacubitril/valsartan and ICD = 0.21

Sacubitril/valsartan's potential mechanism of action for the reduction in sudden deaths

Effects of angiotensin-neprilysin inhibition as compared to angiotensin inhibition on ventricular arrhythmias in reduced ejection fraction patients under continuous remote monitoring of implantable defibrillator devices

de Diego et al. Heart Rhythm 2018;15(3):395-402

Study design and patient population



Patient population:
120 HFrEF patients with ICD or ICD-CRT referred to cardiology HF/arrhythmia outpatient clinic:

- HF symptoms with NYHA class ≥II despite optimal medical therapy, including initiation and titration of ACEi (ramipril) or ARB (valsartan), β-blockers, and MRA if tolerated
- LVEF ≤40%
- Under home monitoring of an ICD
- Patients serve as their own control by design

1. de Diego et al. Heart Rhythm. 2018;15(3):395-402

Patient characteristics pre- and post-intervention (1/3)

- Study design ensured patients served as their own controls[1]

	Pre-ARNI (n = 120)	Post-ARNI (n = 120)	P value
Clinical characteristics			
Age (yrs)	69 ± 8	70 ± 8	NS
Male	91 (76)	91 (76)	NS
Ischemic cardiopathy	98 (82)	98 (82)	NS
Hypertension	75 (62)	75 (62)	NS
Diabetes	36 (30)	36 (30)	NS
Hypercholesterolemia	62 (52)	63 (52)	NS
Renal insufficiency (filtration rate <60 mL/min)	48 (40)	48 (40)	NS
Rhythm			
Sinus rhythm	85 (71)	84 (70)	NS
Paroxysmal AF	17 (14)	12 (10)	.07
Permanent AF	35 (29)	36 (30)	NS

Values are given as mean ± SD, n (%), or %.

1. de Diego et al. Heart Rhythm. 2018;15(3):395-402;

Patient characteristics pre- and post-intervention (2/3)

- Patients were on OMT throughout the study period
- An improvement in NYHA functional class and a reduction in the dose of diuretic treatment were observed post-ARNI

	Pre-ARNI (n = 120)	Post-ARNI (n = 120)	P value
Medical treatment	100% ACEi or ARB	100% sacubitril-valsartan	
β-blocker	98%	98%	NS
Mineraloid antagonist	97%	97%	NS
Antiarrhythmic drug	30%	29%	NS
Oral diuretic	75%	52%	<.03
Device			
ICD only	56%	56%	NS
ICD + CRT	44%	44%	NS
Primary prevention	65%	65%	NS
Secondary prevention	35%	35%	NS
Clinical data			
NYHA functional class (I–IV)	2.4 ± 0.4	1.5 ± 0.7	<.0002

Values are given as mean ± SD, n (%), or %

1. de Diego et al. Heart Rhythm. 2018;15(3):395-402

Patient characteristics pre- and post-intervention (3/3)

- There was a significant increase in LVEF and LVEDD post-ARNI[1], suggesting both functional and structural improvements in cardiac tissue[1-3]
- Levels of pro-BNP were lowered post-ARNI[1], potentially leading to a reduction in myocardial wall stress and a lower likelihood of ICD shocks[1,4]

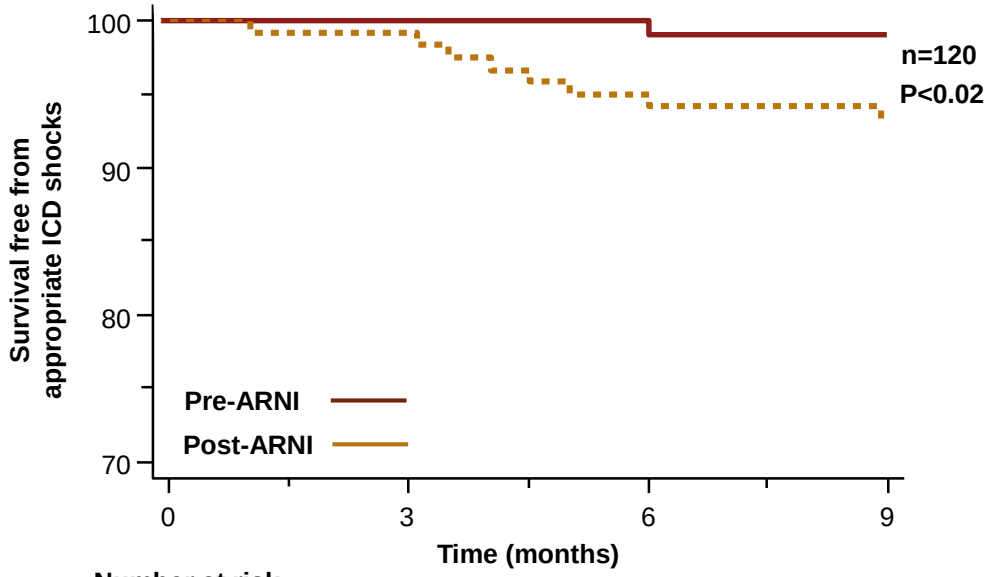
	Pre-ARNI (n = 120)	Post-ARNI (n = 120)	P value
Echocardiographic data			
LVEF (%)	30.4 ± 4	35.1 ± 8	<.01
LVEDD (mm)	61 ± 5	58 ± 6	<.01
Examination data			
Systolic blood pressure (mmHg)	121 ± 38	107 ± 39	<.02
Diastolic blood pressure (mmHg)	73 ± 23	64 ± 26	<.006
Heart rate average (bpm)	67 ± 7	64 ± 5	<.006
Blood tests			
Potassium level (mEq/L)	4.4 ± 0.5	4.7 ± 0.5	<.03
Pro-BNP (pg/mL)	1971 ± 1530	1172 ± 955	<.01
Glomerular filtration rate (mL/min)	55 ± 19	57 ± 19	NS

Values are given as mean ± SD, n (%), or %

1. de Diego et al. Heart Rhythm. 2018;15(3):395-402; 2. Al-Khatib et al. Circulation. 2017;000:e000–e000. DOI: 10.1161/CIR.0000000000000549; 3. Tomaselli , Zipes. Circ Res. 2004;95:754-63; 4. Levine et al. Heart Rhythm 2014;11:1109–1116

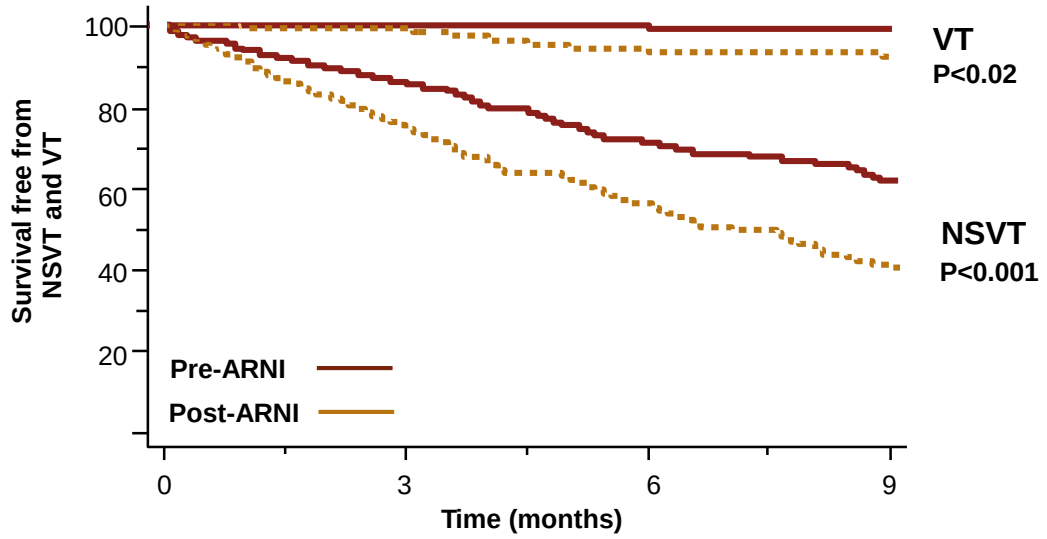
Sacubitril/valsartan significantly increased survival free time from appropriate ICD shocks, compared with ACEi/ARB

- The most common mechanism of sudden death in patients with an ICD was VT/VF treated with an appropriate shock followed by EMD[2]
- ICD patients suffer from poorer psychological well-being following shocks, which impacts QoL[3-5]



1, de Diego et al. Heart Rhythm. 2018;15(3):395-402; 2. Mitchell et al. J Am Coll Cardiol. 2002;39:1323– 8; 3. Tomzik et al. Front Cardiovasc Med. 2015;234. doi: 10.3389/fcvm.2015.00034; 4. Passman, et al. Arch Intern Med 2007;167(20):2226-32.
5. Mark et al. New Engl J Med. 2008;359(10):999-1008; Figure from de Diego et al

Sacubitril/valsartan significantly increased survival free time from VT and NSVT, compared with ACEi/ARB



Number at risk (VT)

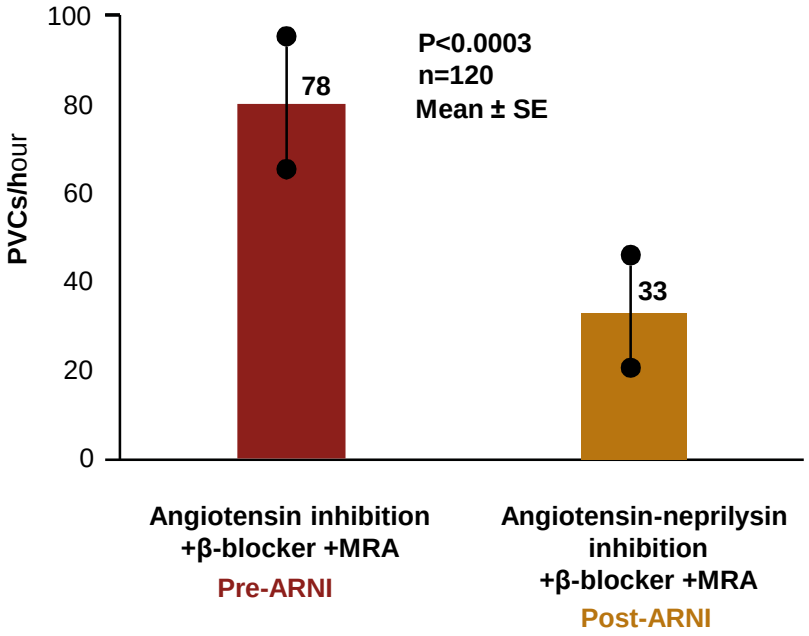
ARNI	120	120	120	120	119	119
ACEi/ARB	120	119	119	115	113	113

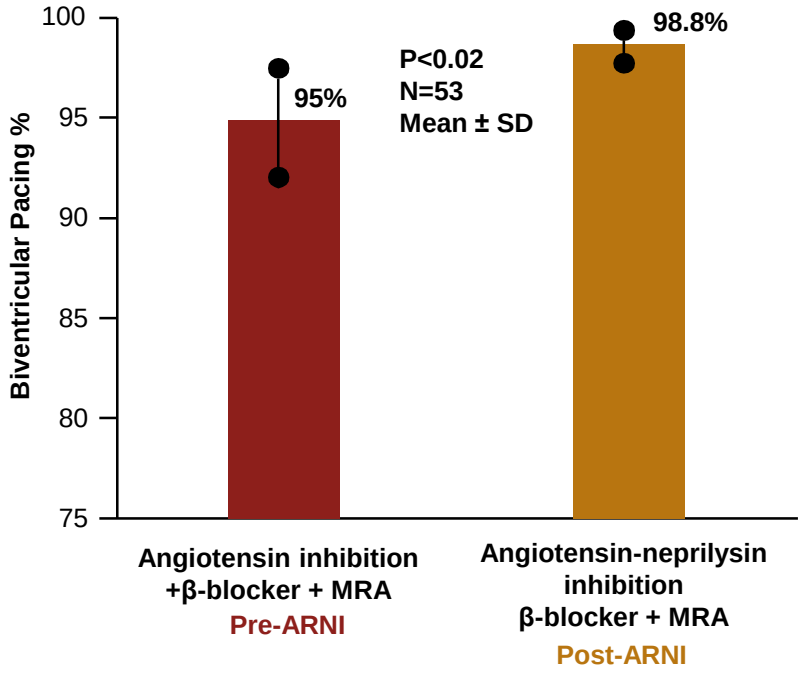
Number at risk (NSVT)

ARNI	120	111	103	95	86	82
ACEi/ARB	120	104	90	77	67	59

1. de Diego et al. Heart Rhythm. 2018;15(3):395-402

A decrease in PVC burden after sacubitril/valsartan was associated with an increase in biventricular pacing %, compared with ACEi/ARB





1. de Diego et al. Heart Rhythm. 2018;15(3):395-402

Optimization of medical therapy is necessary to improve outcomes in HF patients, whether or not they have an ICD

Summary (1/2)

- In patients with HFrEF (LVEF ≤40%), OMT is recommended to reduce sudden death and all-cause mortality
  - If LVEF remains <35% after OMT, guideline recommendations advise the use of ICD in symptomatic patients
- Despite OMT and use of ICD, many patients remain at a high risk of sudden death (especially NYHA class II patients)
- In PARADIGM-HF:
  - 44.8% of NYHA class II HF CV deaths were sudden deaths
  - Sacubitril/valsartan decreased the risk of sudden death by 20% vs enalapril
    - For patients on an ICD, sacubitril/valsartan showed a 51% relative risk reduction vs enalapril
- Sacubitril/valsartan has a class IA recommendation for the pharmacological prevention of sudden death (as part of triple therapy)

Summary (2/2)

- deDiego et al (2018) have shown that, in patients with an ICD and remote monitoring, switching ACEi/ARB to sacubitril/valsartan *significantly decreases*:
  - Ventricular arrhythmias
  - ICD shocks
  - PVC burden

  And significantly increases:
  - Biventricular pacing percentage
- *This mechanistic study provides a potential explanation for the observed reduction in sudden death seen in PARADIGM-HF*

CẢM ƠN SỰ THEO DÕI CỦA QUÝ ĐỒNG NGHIỆP